Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000257

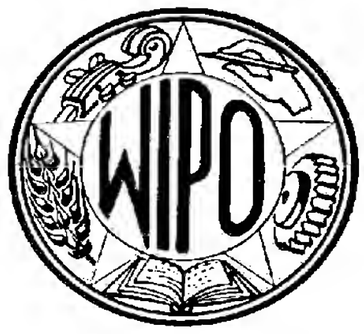
International filing date: 03 March 2005 (03.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/549,550
Filing date: 04 March 2004 (04.03.2004)

Date of receipt at the International Bureau: 15 March 2005 (15.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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PCT/IL2005/000257
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APPLICATION NUMBER: *60/549,550*
FILING DATE: *March 04, 2004*

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Express Mail Label No.

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Additional inventors are being named on the _____ separately numbered sheets *attached hereto*

TITLE OF THE INVENTION (500 characters max)

STRUCTURED TRIGLYCERIDES AND EMULSIONS COMPRISING SAME

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification *Number of* Pages 29
☐ Drawing(s) *Number of* Sheets _____
☐ Application Date Sheet. See 37 CFR 1.76
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Date March 4, 2004

REGISTRATION NO. 45,148 (*if* appropriate)

Docket Number: 1299-USP

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PROVISIONAL PATENT APPLICATION

STRUCTURED TRIGLYCERIDES AND EMULSIONS COMPRISING SAME

Inventors: Irit Shochat and Geila Rozen

FIELD OF INVENTION

The present invention relates to structured triglycerides, to parenteral nutrition emulsions comprising same, and use thereof. In particular, the invention relates to structured triglycerides comprising at least one medium chain C_6-C_{12} fatty acid and at least one fatty acid selected from long chain C_{14}-C_{18} or very long chain C_{20}-C_{22} fatty acids, preferably each fatty acid being in a predetermined position of the glycerol backbone. The parenteral nutrition emulsions are particularly useful for nourishing preterm and term infants, children, critically ill patients, and cancer patients.

BACKGROUND OF THE INVENTION

Lipids have been used as an integral component of parenteral nutrition over the last four decades. Lipids provide essential fatty acids for cellular structures, specifically cell membranes, and for precursors of prostaglandins, leukotrienes, thromboxanes and other eicosanoids. They constitute a source of energy, take part in various biosynthetic pathways, and are carriers of fat-soluble vitamins. As such, lipids play an important role in metabolic and immune processes, in the development and function of the central nervous system and the retina.

Fatty acids (FA) differ from one another by the number of carbon atoms, their saturation or degree of non-saturation, the positions of unsaturated bonds, and whether these bonds are cis or trans. All of these variables are relevant to the nutritional value or benefit derived from triglycerides containing these acids. In addition, the enzymatic cleavage of the triglycerides is affected by the type and position of the fatty acids on the glycerol backbone.

Fatty acids in general are divided into four groups: short chain FA, medium chain FA (MCFA), long chain FA (LCFA), and very long chain FA (VLCFA). Fatty acids are

also classified by the presence, number, and location of double bonds. This classification divides FA into three groups: saturated FA (no double bonds), monounsaturated FA (one double bond) and polyunsaturated FA (2 double bonds and more). Further classification of the polyunsaturated FA is characterized by the placement of the carbon preceding the first double bond from the terminal methyl carbon: n-3 or ω-3 FA, n-6 or ω-6 FA and n-9 or ω-9 FA. These differences determine the various characteristics of FA and therefore their specific functions.

Lipid emulsions

The need for lipids as essential and integral component of parenteral nutrition (PN) emerged from the observations of the clinical symptoms following use of fat free PN. These clinical symptoms included hemorrhagic dermatitis, skin atrophy, hyperglycemia, weight loss, decrease of immune function, increase of catabolism, etc.

The first generation of lipid emulsions was based on pure long chain triglycerides (LCT) derived from soybean oil and safflower oil. Their administration prevented some of the symptoms of fatty acid deficiency. Nevertheless, patients that received these lipid emulsions showed impaired function of lymphocytes and of the reticuloendothelial system, depressed T-cell counts, increased oxygen free radical production, elevation of liver enzymes, hypertriglyceridemia, and suffered from infections (1-6).

The next generation of lipid emulsions contained 50% medium chain triglycerides MCT/LCT emulsions. These emulsions have many advantages compared to pure LCT emulsions, for example, they are efficient energy source, more soluble, rapidly hydrolyzed by lipases, quickly eliminated from blood, rapidly oxidized, and have smaller particle size. As the MCFA are all saturated, they are not subjected to peroxide formation and therefore they do not impair the immune and reticuloendothelial systems. Patients receiving MCT/LCT emulsions demonstrate a better nitrogen balance and a better protein sparing effect (5, 7, 8).

Another attempt to overcome the disadvantages of pure LCT emulsions was to use olive oil, rich in monounsaturated oleic acid (18:1 ω-9). Olivier et al. showed that olive oil based emulsions were well-tolerated, more suitable for preventing lipid peroxidation, and maintained a normal essential FA status (9). It was also demonstrated that olive oil emulsions contain primarily alpha tocopherol, the more biologically active tocopherol, while soybean oil emulsions contain predominantly gamma tocopherol, which has little protection against lipid peroxidation. Antebi et al., compared the composition and peroxidability of lipoproteins in children receiving olive oil or soybean

oil emulsions and showed a decreased oxidative stress following olive oil administration. Koletzko et al., and Goulet et al., showed the advantages of olive oil emulsions compared to LCT emulsions in preterm and term infants and in children (10, 11). The oleic acid, and in general the ω-9 fatty acids, have been shown to contribute to brain development and function as they are a major component of the white matter and myelin (12).

The beneficial effects of ω-3 fatty acids, derived from fish oil, in enteral feeding prompted their inclusion in parenteral nutrition. The most successful regimen was achieved by the combination of 50% MCT, 40% soybean oil and 10% fish oil. This regimen demonstrated an improvement in the immune system function of surgical and critically ill patients, an improvement of FA profile in cell membranes, anti-inflammatory and anti-coagulation effects, a normalization of plasma triglycerides (TG) and cholesterol, and a reduction in blood pressure (13-21).

Structured triglycerides

Lipid emulsions containing randomized structured triglycerides (STG) have been obtained by mixing MCT and LCT oils and heating the mixture in the presence of a catalyst. During this process, fatty acids of different chain lengths can be esterified into one triglyceride molecule. The new TG contains both long and medium chain FA, on the same glycerol, randomly distributed. This kind of triglycerides is rapidly hydrolyzed by lipases, and hence is better cleared from the blood stream.

Many clinical studies have demonstrated the safety and the advantages of STG emulsions. Sandstron et al., demonstrated that STG emulsions administered to postoperative patients were rapidly cleared from the plasma, rapidly oxidized, and were not associated with any side effects. Provision of STG caused a significantly higher whole body fat oxidation compared to LCT (22). Rubin et al, demonstrated that STG appear to be safe and well tolerated on a long term basis in patients on home parenteral nutrition and suggested that STG emulsions may be associated with possible reduction in liver dysfunction (23).

Kruimel et al., compared the effect of STG versus physical mixture of MCT and LCT on the nitrogen balance of moderately catabolic postoperative patients. Over a period of 5 days the cumulative nitrogen balance was less negative in the STG group. This difference can be explained by a better utilization of the STG fatty acids for energy and a better clearance from the blood (24). Chambrier et al., compared the effect of STG vs. a physical mixture of MCT-LCT on liver function in postoperative patients. A

significant increase in liver enzymes and in plasma TG was found to occur in patients administered with the physical mixture of MCT-LCT, while no changes in liver function nor in plasma TG level were found to occur in patients administered with STG (25).

U.S. Pat. No. 4,871,768 discloses a synthetic triglyceride comprising a glycerol backbone having three fatty acids attached thereto, wherein at least one fatty acid is selected from ω3 fatty acids and at least one fatty acid is selected from C_8-C_{10} fatty acids. The ω3 fatty acids are derived from plant oils, marine plankton oils, fungal oils, or fish oils. U.S. Pat. No. 4,871,768 also discloses a dietary supplement comprising 10 to 40% by weight of a lipid fraction, the lipid fraction comprises 10 to 90% by weight of the synthetic triglyceride. The dietary supplement according to U.S. Pat. No. 4,871,768 further comprises ω9 fatty acids and a small quantity of ω6 fatty acids. Yet, the necessity of docosahexaenoic (DHA) and vitamin E has not been indicated in the dietary supplement nor the optimal ratio of ω6 to ω3.

U.S. Pat. No. 4,906,664 discloses a method for providing nutritional support to patients suffering from cancer cachexia. The method comprises the step of parenteral administration of a diet containing a structured lipid. The structured lipid according to U.S. Pat. No. 4,906,664 is a triglyceride where at least one of the chains is a medium chain fatty acid, and the two other chains are selected from medium chain fatty acids and long chain fatty acids. The ratio of long chain fatty acids to medium chain fatty acids is about 1:1. The long chain fatty acids should be primarily ω3 and ω6 fatty acids, with sufficient ω6, preferably in the form of linoleic acid.

U.S. Pat. No. 5,081,105 discloses a method of treating sarcomas in a patient through the use of nutritional support therapy comprising the step of parenterally administering a diet including a structured lipid. The structured lipid according to U.S. Pat. No. 5,081,105 is a triglyceride where one of the chains is a medium chain fatty acid, a second chain is a ω3 fatty acid, and the third chain is selected from H, OH, short, medium, and long fatty acids.

U.S. Pat. No. 5,962,712 discloses a family of structured lipids wherein at least one of the fatty acid residues is selected from gamma linolenic acid (GLA) and dihomogamma linolenic acid (DHGLA). In addition to the first fatty acid residue selected from GLA and DHGLA, a second fatty acid residue is selected from C_{18}-C_{22} n-3 fatty acids, and the third fatty acid residue is selected from C_6-C_{12} fatty acids. The

simultaneous presence of C_{18}-C_{22} n-3 fatty acid residues may serve to minimize the elongation of GLA and DHGLA to arachidonic acid. The long chain polyunsaturated n-3 fatty acids will purportedly shift the prostaglandin metabolism away from pro-inflammatory prostanoids to non-inflammatory prostanoids, having beneficial effects in treating inflammation and infection. U.S. Pat. No. 5,661,180 discloses a method of modulating metabolic response to trauma and disease states in a patient comprising the step of administering a dietary structured lipid as disclosed in U.S. Pat. No. 5,962,712.

There is an unmet need for structured triglycerides designed to provide improved enteral or parenteral nutrition, which is easily assimilated by infants, children, and patients suffering severe stress or chronic illness and which is optimized to address developmental and immunological needs.

SUMMARY OF THE INVENTION

It is now disclosed that parenteral nutrition emulsions comprising structured triglycerides comprising medium chain (MCFA), long chain (LCFA), and very long chain fatty acid residues (VLCFA), are highly advantageous for parenteral nutrition, particularly for preterm and term infants, children, critically ill patients, and cancer patients. Accordingly, the present invention provides parenteral nutrition emulsions comprising triglycerides comprising specific beneficial ratios of MCFA, LCFA and VLCFA.

According to the principles of the present invention, the parenteral nutrition emulsions comprise structured triglycerides wherein the position of the fatty acid residues on the glycerol backbone is predetermined.

According to the principles of the present invention, it is disclosed herein, for the first time, that parenteral nutrition emulsions comprising structured triglycerides comprising the essential VLCFA, i.e., arachidonic acid (AA; 20:4 ω-6), eicosapentaenoic acid (EPA; 20:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3), wherein the VLCFA esterified primarily at the external position of the glycerol backbone, said emulsions provide high nutritional advantage, improve immune system function, and have beneficial effects on the structure of cell membranes, CNS, and retina, on cardiac activity, and on coagulation processes. In addition, the parenteral nutrition emulsions of the invention are very useful in brain and retina development in preterm and term infants as well as in children.

It is also disclosed that a low ratio of ω-6 to ω-3 fatty acids, particularly an ω-6/ω-3 ratio lower than 2:1, in the structured triglycerides and in the parenteral nutrition emulsions comprising same provides unexpectedly beneficial effects in brain development in preterm-, term infants, and children. The low ω-6/ω-3 ratio also provides beneficial effects in resistance to infections and to heart problems in critically ill patients, in cancer patients, and in patients suffering from immunosuppression. It will be understood that a decrease of the ω-6 fatty acids intake and an increase of the ω-3 fatty acids with no supplementation of AA may alter and impair some biological processes such as coagulation, bleeding time, and immune function, and therefore, it is advantageous to include AA in the structured triglycerides of the invention.

In addition, it is disclosed that inclusion of monounsaturated oleic acid (18:1 ω-9) in the structured triglycerides provides superior properties compared to polyunsaturated fatty acids as the former is less susceptible to peroxide formation and hence is less involved in peroxidation damages.

It is also disclosed that addition of vitamin E, particularly alpha tocopherol, to the lipid emulsions provides protection of the subject nourished with said parenteral nutrition emulsions against peroxide formation, and therefore protects the subject from peroxidation damages.

According to one aspect, the present invention provides a structured triglyceride comprising a glycerol backbone having three fatty acid residues esterified thereto, wherein at least one fatty acid residue is selected from the group consisting of C_6-C_{12} fatty acids and active derivatives thereof, and at least one fatty acid residue is selected from the group consisting of C_{14}-C_{18} fatty acids, C_{20}-C_{22} fatty acids, and active derivatives thereof, with the proviso that a C_{18}-C_{22} ω-3 fatty acid residue is not present on the same glycerol backbone together with gamma linolenic acid or dihomogamma linolenic acid.

According to one embodiment, the at least one C_6-C_{12} fatty acid is selected from caproic acid, caprilic acid, capric acid, and lauric acid. In a currently preferred embodiment, the C_6-C_{12} fatty acid is selected from caprilic acid (8:0), and capric acid (10:0).

According to another embodiment, the at least one C_{14}-C_{18} fatty acid is selected from saturated, monounsaturated, and polyunsaturated fatty acids. Preferably, the C_{14}-C_{18} fatty acid is selected from palmitic acid (16:0), stearic acid (18:0), oleic acid (18:1 ω-9), linoleic acid (18:2 ω-6), and alpha linolenic acid (18:3 ω-3).

According to another embodiment, the at least one C_{20}-C_{22} fatty acid is selected from the group consisting of, but not limited to, arachidonic acid (20:4 ω-6), ardenic acid (22:4 ω-6), docosapentaenoic acid (22:5 ω-6), eicosapentaenoic acid (20:5 ω-3), and docosahexaenoic acid (22:6 ω-3). In a currently preferred embodiment, the C_{20}-C_{22} fatty acid is selected from arachidonic acid (AA; 20:4 ω-6), eicosapentaenoic acid (EPA; 20:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3).

According to another aspect, the present invention provides a structured triglyceride comprising a glycerol backbone having three fatty acid residues esterified thereto, where at least one fatty acid residue is selected from the group consisting of C_6-C_{12} fatty acids and active derivatives thereof in the internal position of the glycerol backbone, and at least one fatty acid residue is selected from the group consisting of C_{14}-C_{18} fatty acids, C_{20}-C_{22} fatty acids, and active derivatives thereof in an external position of the glycerol backbone.

According to one embodiment, the at least one C_6-C_{12} fatty acid is selected from caproic acid, caprilic acid, capric acid, and lauric acid. In a currently preferred embodiment, the C_6-C_{12} fatty acid is selected from caprilic acid (8:0), and capric acid (10:0).

According to another embodiment, the at least one C_{14}-C_{18} fatty acid is selected from saturated, monounsaturated, and polyunsaturated fatty acids. Preferably, the C_{14}-C_{18} fatty acid is selected from palmitic acid (16:0), stearic acid (18:0), oleic acid (18:1 ω-9), linoleic acid (18:2 ω-6), and alpha linolenic acid (18:3 ω-3).

According to another embodiment, the at least one C_{20}-C_{22} fatty acid is selected from the group consisting of, but not limited to, dihomogamma linolenic acid (20:3 ω-6), arachidonic acid (20:4 ω-6), ardenic acid (22:4 ω-6), docosapentaenoic acid (22:5 ω-6), eicosapentaenoic acid (20:5 ω-3), and docosahexaenoic acid (22:6 ω-3). In a currently preferred embodiment, the C_{20}-C_{22} fatty acid is selected from arachidonic acid (AA; 20:4 ω-6), eicosapentaenoic acid (EPA; 20:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3).

According to another aspect, the present invention provides a parenteral nutrition emulsion composition comprising a structured triglyceride of the invention.

According to one embodiment, the C_6-C_{12} fatty acids are from about 9 to 90% by weight of total fatty acids of the parenteral nutrition emulsion composition. Preferably, the C_6-C_{12} fatty acids are from about 30 to 60% by weight of total fatty acids, and more preferably, from about 40 to 50% by weight of total fatty acids. In a currently preferred

embodiment, caproic acid (6:0), caprilic acid, capric acid, and lauric acid (12:0) are 2.5%, 30%, 10%, and 2.5% by weight, respectively, of total fatty acids of the parenteral nutrition emulsion composition.

According to another embodiment, the C_{14}-C_{18} fatty acids are from about 9 to 90% by weight of total fatty acids of the parenteral nutrition emulsion composition. Preferably, the C_{14}-C_{18} fatty acids are from about from about 40 to 70% by weight of total fatty acids, and more preferably from about 40 to 50% by weight. In a currently preferred embodiment, the palmitic acid, stearic acid, oleic acid, linoleic acid, and alpha linolenic acid are 10%, 2.5%, 15%, 16%, and 7% by weight, respectively, of total fatty acids of the parenteral nutrition emulsion composition.

The C_{20}-C_{22} fatty acids according to the invention are from about 1 to 20% by weight of total fatty acids of the parenteral nutrition emulsion composition, preferably from about 1 to 10%, and more preferably from about 1 to 5%. In a currently more preferred embodiment, AA, EPA, and DHA each is 1.5% of total fatty acids of the parenteral nutrition emulsion composition. It will be understood that it is highly essential to combine the fatty acids disclosed herein in one parenteral nutrition emulsion in order to cover the patient's needs. It will be appreciated that the parenteral nutrition emulsion compositions of the invention may comprise triglycerides wherein the three fatty acid residues esterified to the glycerol backbone are all selected from C_6-C_{12} fatty acids.

According to the invention, a ratio of ω-6/ω-3 fatty acids of the parenteral nutrition emulsion composition is be lower than 7:1, preferably lower than 4:1, more preferably lower than 2:1. In a currently preferred embodiment, the ratio of ω-6/ω-3 fatty acids of the parenteral nutrition emulsion composition is about 1.75:1. The present invention thus also encompasses ratio of ω-6 to ω-3 fatty acids of 1:1.

According to another embodiment, the parenteral nutrition emulsion composition comprises 10 to 40% (w/v) of the structured triglycerides of the invention. More preferably, the parenteral nutrition emulsion composition comprises 15 to 30% (w/v) of the structured triglycerides of the invention, and most preferably the parenteral nutrition emulsion composition comprises 20 to 25% (w/v) of the structured triglycerides of the invention. In a currently preferred embodiment, the parenteral nutrition emulsion composition comprises 20% (w/v) of the structured triglycerides of the invention.

According to another embodiment, the parenteral nutrition emulsion composition must comprise vitamin E, preferably alpha tocopherol. The parenteral nutrition

emulsion of the invention may comprise 0.1 to 20 mg of alpha tocopherol per 1 gr of fatty acids. Preferably, the parenteral nutrition emulsion may comprise 1 to 5 mg of alpha tocopherol per 1 gr of fatty acids. In a currently preferred embodiment, the parenteral nutrition emulsion comprises 1.8 mg of alpha tocopherol per 1 gr of fatty acids.

The parenteral nutrition emulsion composition according to the invention may further comprise an emulsifier. The amount of phospholipids in the parenteral nutrition emulsion composition may range from 0.5 to 4% (w/v). Preferably, the amount of phospholipids is from about 0.5 to 2.5% (w/v). In a currently preferred embodiment, the parenteral nutrition emulsion composition comprises 1-1.2% (w/v) of phospholipids.

According to the invention, the parenteral nutrition emulsion composition may also comprise an osmolality modifier. A preferred osmolality modifier is glycerin. The amount of an osmolality modifier may range from 1 to 5% (w/v), preferably from 1 to 3% (w/v).

The parenteral nutrition emulsion composition may further comprise carbohydrate nutrients, electrolytes, amino acids, vitamins, trace minerals, and a preservative. The parenteral nutrition emulsion composition may also comprise sterile water.

The preferred ranges of ingredients of parenteral nutrition emulsion compositions according to the invention are: Structured triglycerides are about 20% (w/v), the MCFA are about 45% by weight of total fatty acids, LCFA are about 50% by weight of total fatty acids, and VLCFA are about 5% by weight of total fatty acids wherein the ratio of ω-6 to ω-3 fatty acids is 1.75; phospholipids – about 1.2% (w/v).

According to another aspect, the present invention provides a method of providing nutrition to a subject in need thereof comprising parenterally administering to the subject a parenteral nutrition emulsion composition of the invention.

According to one embodiment, the subject to be nourished by the parenteral nutrition emulsion composition of the invention is selected from the group consisting of preterm and term infants, children, critically ill patients, cancer patients, and patients suffering from surgical trauma, burns, malnutrition, starvation, aging, and immunosuppression. Preferably, the subjects to be nourished by the parenteral nutrition emulsion of the invention are preterm and term infants, critically ill patients, and patients suffering from AIDS.

These and other embodiments of the present invention will be better understood in relation to the description, examples, and claims that follow.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides structured triglycerides and parenteral nutrition emulsions comprising same to be used in parenteral nutrition of preterm and term infants, critically ill patients, and cancer patients.

According to one aspect, the present invention provides a structured triglyceride comprising a glycerol backbone with three fatty acid residues linked thereto, where at least one fatty acid residue is selected from medium chain fatty acids and active derivatives thereof, and at least one fatty acid residue is selected from long chain fatty acids, very long chain fatty acids, and active derivatives thereof, with the proviso that a C_{18-22} ω-3 fatty acid residue is not present on the same glycerol backbone together with gamma linolenic acid or dihomogamma linolenic acid.

The term "active derivatives" as used herein includes esters, ethers, amines, amides, substituted fatty acids (e.g., halogen substituted fatty acids), and other substitutions, which do not affect the beneficial properties of the structured triglyceride.

The structured triglycerides of the invention are made as "designer oil". Using enzymatic procedures known in the art that direct the incorporation of specific fatty acids to specific positions in the glycerol molecule, structured triglycerides are synthesized.

U.S. Pat. No. 6,537,787, the content of which is incorporated herein as if fully set forth, discloses a method for obtaining a mixture enriched with polyunsaturated fatty acid triglycerides in the presence of a position-specific lipase, particularly 1,3-specific lipase. The specific lipase according to U.S. Pat. No. 6,537,787 is preferably a lipase of Candida antartica.

U.S. Pat. No. 6,518,049, the content of which is incorporated herein as if fully set forth, discloses a method for esterification of marine oil compositions, which contain EPA and DHA as free acids, with glycerol in the presence of a lipase catalyst under reduced pressure and essentially organic solvent-free conditions to form a fatty acid fraction enriched in at least one of EPA and DHA. According to U.S. Pat. No. 6,518,049 the lipase is preferably immobilized on a carrier and is Rhizomucor meihei.

Sugihara et al. (Appl. Microbiol. and Biotech. 1993 40:279-83 and references cited therein) disclosed a microorganism having a moderate selectivity towards the *sn*-2 position in glycerides. Ota et al. (Biosci. Biotechnol. Biochem. 2000, 64: 2497) disclosed an enzyme of *Geotrichum candidum*, which hydrolyzes the *sn*-2-positioned ester bond nearly twice more as compared to hydrolysis of the 1- or 3-positioned ester bonds.

U.S. Pat. No. 6,605,452 to Basheer discloses a lipase preparation immobilized onto an insoluble matrix that preferably has 1,3-positional specificity with respect to triacylglycerols, the content of which is incorporated herein as if fully set forth. Thus, a lipase preparation comprising an insoluble matrix or a surfactant-coated lipase complex immobilized onto an insoluble matrix may be used for preparing structured triglycerides of the present invention. The lipase may be derived from any source, but preferably, the lipase is obtained from a microorganism. Many different species of microorganisms may be used as a source of lipase for the lipase preparation of the invention. The invention, however, is particularly directed to the use of lipase that is derived from a species selected from the group consisting of Burkholderia sp., Candida antractica B, Candida rugosa, Pseudomnonas sp., Candida antractica A, Porcine pancreas lipase, Humicola sp., Mucor miehei, Rhizopus javan., Pseudomonas fluor., Candida cylindrcae, Aspergillus niger, Rhizopus oryzae, Mucor jaanicus, Rhizopus sp., Rhizopus japonicus and Candida antractica.

The surfactant in the surfactant-coated lipase complex may include a fatty acid conjugated to a hydrophilic moiety. The fatty acid may be monolaurate, monomyristate, monopalmitate, monostearate, dilaurate, dimyristate, dipalmitate, distearate, trilaurate, trimyristate, tripalmitate and tristearate. The hydrophilic moiety may be a sugar, a phosphate group, a carboxylic group, and a hydroxylated organic residue. Examples of sugar to be used include sorbitol, sucrose, glucose, lactose, and a like. The fatty acid and the hydrophilic moiety may be linked by any suitable type of bond. However, it is preferred that the fatty acid and the hydrophilic moiety may be conjugated via an ester bond.

The content of the lipase may be 2-20 weight percent of the surfactant-coated lipase complex. Preferably, the content of the lipase may be 0.01-1.0 weight percent of the preparation.

Many types of matrix may be used for immobilization of the lipase preparation. Examples of matrices are inorganic insoluble matrices and organic insoluble matrices

including, but not limited to, calcium carbonate, alumina, calcium sulfate, ion-exchange resin, such as, for example, Amberlite® and Dowex®, silica gel, charcoal, Eupergit®, ethylsulfoxycellulose, and aluminium stearate.

Structured triglycerides may be prepared by esterification, acidolysis, trans-esterification, inter-esterification or alcoholysis between two fatty acids using a lipase preparation comprising an insoluble matrix or an insoluble matrix-immobilized surfactant-coated lipase complex. Contacting the lipase, particularly the matrix-immobilized surfactant-coated lipase complex, with the fatty acids may be affected in the presence of an organic solvent. It should also be noted that contacting the lipase, particularly, the matrix-immobilized surfactant-coated lipase complex, with the fatty acids may be affected within a reaction reactor, e.g., a tank reactor or a fixed-bed reactor.

It will be understood that the structured triglycerides of the invention may also be made by any procedure commonly used to make structured lipids generally.

The inclusion of C_6-C_{12} fatty acids in the structured triglycerides has additional benefits. The C_6-C_{12} fatty acids do not need carnitine to enter the mitochondria, thus they are rapidly cleared from blood and are used as energy source. As a component of the structured triglycerides, MCFA contribute to achieve a lower molecular weight, therefore, a better solubility and a better stability of the emulsion.

The terms "ω-3", "ω-6" and "ω-9" define herein a fatty acid in which a double bond is present at the third carbon, sixth carbon, and ninth carbon, respectively, from the methyl end of the hydrocarbon chain. This nomenclature is equivalent to the n-3, n-6, and n-9 designations. The terms ω-3, ω3, n-3; ω-6, ω6, n-6; and ω-9, ω9, and n-9 are used interchangeably throughout the specification and claims of the present invention.

According to the invention, the parenteral nutrition emulsion must comprise vitamin E, preferably alpha tocopherol. The normal range of plasma tocopherol concentrations is between 0.7 and 1.6 mg/100 ml. It should be understood that the recommended amount of vitamin E for premature infants is 4.55 mg/day and for adults 100 – 200 mg/day (35, 36). Vitamin E is classified as a practically non-toxic substance. A dosage below 1000 mg/day is safe and free from side effects (37-41). In order to maintain normal range of tocopherol, vitamin E should be matched quantitatively to unsaturated FA. Therefore, the parenteral nutrition emulsion of the invention may comprise 0.1 to 20 mg of alpha tocopherol per 1 gr of fatty acids. Preferably, the

parenteral nutrition emulsion may comprise 1 to 5 mg of alpha tocopherol per 1 gr of fatty acids.

The parenteral nutrition emulsion composition according to the invention may further comprise an emulsifier such as phospholipids. Examples of phospholipids which may be used in compositions according to the invention are lecithins; EPIKURON 170 (trade name) being a mixture of about 70% (w/v) of phosphatidyl choline, 12% phosphatidyl ethanolamine, and about 16% other phospholipids, or OVOTHIN 160 (trade name) being a mixture comprising about 60% (w/v) phosphatidylcholine, 18% (w/v) phosphatidyl ethanolamine, and (w/v) other phospholipids, both manufactured by Lucas Meyer (Germany). These mixtures of mainly phosphatidylcholine and phosphatidylethanolamine are derived from a natural source, such as purified egg yolk phospholipids (for the Ovothin series) and soybean oil phospholipids (for the Epikuron series); a purified phospholipid mixture; LIPOID E-80 (trade name) being a phospholipid mixture comprising about 80% (w/v) phosphatidylcholine, about (w/v) phosphatidylethanolamine, about 3.6% non-polar lipids, and about 2% sphingomyeline--manufactured by Lipoid KG (Ludwigshafen, FRG).

The parenteral nutrition emulsion composition may further comprise carbohydrate nutrients such as, for example, dextrose; electrolytes such as, for example, potassium and sodium chloride; amino acids; vitamins such as, for example, vitamin A, and vitamin D; trace minerals such as, for example, zinc ions, and a preservative such as, for example, methyl-, ethyl-, propyl-, and butylparaben, which are medically accepted for parenteral administration. The amino acids include essential and non-essential amino acids. The parenteral nutrition emulsion composition may also comprise sterile water.

Generally, lipid droplets in emulsions for medical use should preferably be small, i.e., below about 1 μm, since the smaller the droplets, the more stable in storage is the emulsion. The droplet size is advantageously in the size range of about 0.05 to 0.5 μm, and preferably about 0.1 to 0.3 μm. The droplet size is of particular importance since large droplets will not readily pass through small blood capillaries. The compositions of the invention are particularly suitable for obtaining such small droplets.

The compositions of the present invention may be prepared by a number of ways. By one preparation mode, an aqueous solution and an oily solution are separately prepared, the aqueous solution comprising the phospholipids and optionally also an osmotic pressure regulator and a preservative, and the oily solution comprising the

structured triglycerides, and an antioxidant. The aqueous solution is prepared from two a priori prepared solutions, a first, alcoholic, solution containing the phospholipids and a second solution containing in water the other optional ingredients mentioned above. The said aqueous solution is then prepared by mixing the first and the second solution, then removing the alcohol, for example by evaporation, to yield the said aqueous solution.

The aqueous solution and the oily solution are then mixed with one another. However, the so-obtained mixture does not yet consist of sufficiently small droplets, the size of which (obtained after mixing with a magnetic stirrer) is about 10 μm. The droplet size of the inventive composition may then be decreased by the use of emulsification equipment such as Ultra Turrax (Jankl and Kunkel, Staufen, FRG), which yields droplets having an average diameter of about 1.1 μm, or of a high shear mixer, e.g. Polytron (Kinematica, Lucerne, Switzerland), which yields droplets having an average diameter of about 0.65 μm.

Especially small droplets are obtained in the inventive compositions when utilizing a two-stage pressure homogenizer in which the crude dispersion is forced under high pressure through the angular space between a spring loaded valve and the valve seat, the second stage being in tandem with the first so that the emulsion is subjected to two very rapid dispersion processes. An example of such an apparatus is the Gaulin Homogenizer (APV Gaulin, Hilversum, The Netherlands). Use of such an apparatus in accordance with the invention yields compositions in which the droplets have an average diameter of about 0.27 μm with a relatively small deviation.

Even smaller droplets may be obtained in accordance with the invention when the emulsification process combines the use of both a Polytron-type high shear mixer followed by homogenization. The droplet size which is obtained in such a combination is about 0.1-0.15 μm. These relatively small size droplets are preferred when the emulsion is to be used for intravenous administration or when the formulation is to be sterilized by filtration.

Another mode to prepare the parenteral nutrition emulsion compositions of the invention is by mixing together a liposome mixture and an oily mixture, each one prepared separately beforehand. The liposome mixture comprises all the ingredients, which in the final composition do not form part of the oily phase, namely the phospholipids, and also the optional osmotic pressure regulator and the preservative. The preparation of the liposome mixture from these ingredients may be carried out by means known in the art.

The oily mixture comprises the structured triglycerides, and also the anti-oxidant.

After the liposome mixture is mixed together with the oily mixture, an emulsion is formed having relatively large droplets, e.g., about 10 μm, which is further processed in a similar manner as described above in connection with the first preparation mode, until an emulsion having fine homogenous droplets is obtained.

Advantages of different classes of fatty acids

The group of medium chain fatty acids (MCFA) includes fatty acids that consist of 6–12 carbon atoms. Their chemical and physical structure makes the MCFA more soluble than long chain fatty acids (LCFA), the latter term denoting fatty acid of 14-22 carbon atoms. All the fatty acids in this group are saturated. Being rapidly oxidized, MCFA are considered as a very good source of energy.

Emulsions containing medium chain triglycerides (MCT) are more stable than those containing pure long chain triglycerides (LCT) (26). As MCT enter the blood stream, lipases cleave the triglycerides hydrolytically to glycerol and free fatty acids. Since MCFA do not need carnitine to enter the mitochondria, the bulk of FA released is immediately taken up by the tissues and rapidly oxidized (27,28). This metabolic pathway enables MCFA to be eliminated from the blood stream more quickly than LCFA, and therefore they do not increase blood triglyceride levels and they have low tendency of incorporation into tissue lipids. Adolf, M. et al., investigated the oxidative utilization of MCT versus LCT, and concluded that MCT have higher oxidative utilization (29). Dennison A. et al, and Ball M.J. demonstrated a better nitrogen balance in patients receiving MCT emulsions versus patients receiving LCT emulsions (30, 31). MCFA are, therefore, used as a rapid energy source, preserve body protein, increase nitrogen retention, decrease gluconeogenesis, and improve nitrogen balance (32-36).

LCFA consist of 14-18 carbon atoms. They can be saturated, monounsaturated or polyunsaturated. Long chain triglycerides are transported in the blood as lipoproteins. Lipoprotein lipase and hepatic lipase hydrolyze LCT to FA and glycerol. The clearance of LCT from the blood is slower than MCT. LCFA enter the mitochondria by carnitine. LCFA function as an energy source by beta oxidation, as precursors of longer chain FA, and as a storage in adipose tissues. The most important LCFA are the linoleic acid (18:2 ω-6) and the alpha linolenic (18:3 ω-3), both considered essential FA since they cannot be synthesized by the human body, and therefore must be provided in the diet.

The group of very long chain fatty acids (VLCFA) includes chains of 20 carbon atoms and more. Most of the VLCFA are polyunsaturated. They are synthesized from

LCFA by elongation process, which involves several enzymes. Among the most important VLCFA are arachidonic (AA), an ω-6 fatty acid, and the docosahexaenoic (DHA), an ω-3 fatty acid, which have been shown to be necessary for normal development and function of the central nervous system (CNS) and the retina. AA and DHA are not only mechanical components of the CNS structure, but are also required for cell signaling systems in neurons. There is evidence linking DHA deficiency to attention deficit and hyperactivity disorders, dyslexia, senile dementia, reduced visual and cognitive function, clinical depression, schizophrenia and other problems of psychological and physiological nature. In addition, the eicosapentaenoic acid (EPA) and the DHA, both ω-3 fatty acids, have been indicated to have beneficial effects on coronary heart disease, hypertension, inflammation, arthritis, psoriasis, and other autoimmune disorders and cancer (12, 37, 38). DHA and AA are also involved in the synthesis of prostaglandins, thromboxanes and leukotrienes (39). Finally, DHA and AA are crucial components of biological cell membranes. It has been well established that fetus, preterm and term infants require these fatty acids for their normal development.

Incorporation rates of DHA and AA in red blood cell membranes of infants were shown to decline without supplementation of DHA and AA. Infants fed with human milk (which contain DHA and AA) or formula supplemented with those fatty acids, maintained normal rates of incorporation (40). It was also shown that term and preterm infants fed with formula containing VLCFA exhibit better cognitive behavior and psychomotor development than term and preterm infants fed with formula that did not contain VLCFA (41).

The effect of VLCFA ω-3, like DHA and EPA, on the immune system has been studied in animals and humans. Surgical patients that were given parenteral nutrition including DHA and EPA showed a rise in interleukin 2 (42). Patients having inflammatory bowel diseases who received parenteral or enteral nutrition containing DHA and EPA, showed an improvement in their clinical state with a reduction of the steroid intake (43-45). These beneficial effects of VLCFA ω-3 on inflammatory diseases is presumably due to their involvement in interleukin production, which suppress inflammatory processes.

The VLCFA ω-3 have also been shown to exert beneficial effect on coronary heart diseases as they reduce platelet aggregation and blood viscosity, increase capillary flow, and reduce the risk of myocardial infarction. It should be appreciated that the rate of conversion of these very long chain fatty acids from their precursors is not adequate

to fulfill the body requirements, and therefore such fatty acids have to be included in parenteral nutrition.

According to the invention, the parenteral nutrition emulsion compositions comprising structured triglycerides will comprise ω-6 fatty acids, in at least part of the triglycerides incorporated into the emulsion. It should be appreciated that among the ω-6 fatty acids, AA is included among the currently preferred ω-6 fatty acids. Although the parenteral nutrition emulsion compositions may comprise any ω-6 fatty acid within the structured triglycerides, gamma linolenic acid and dihomogamma linolenic acid will not be present simultaneously on the same glycerol backbone with C_{18-22} n-3 fatty acid residue, in the compositions of the present invention.

Vitamin E

Vitamin E is the nutritional designation of the tocopherols, a group of essential biologically active substances. The various tocopherols are found in germinal cells of plants, in egg yolk, and in meat. The natural tocopherols include four isomers: alpha, beta, gamma, and delta. The most biologically active vitamin E is the alpha tocopherol isomer.

Consumption of fatty acids containing double bonds increases the hazard of peroxide formation, which leads to structural changes within cellular membranes. These changes are demonstrated particularly in impairment of the immune system function, in pulmonary complications, and in increased hemolysis.

Preterm infants and critically ill patients are more vulnerable to peroxidation hazards (46-49).Vitamin E is a highly effective antioxidant, protecting the double bonds of unsaturated fatty acids from oxidative destruction. This protective function is demonstrated both in vitro, in lipid emulsions, and in vivo, by protecting the lipid fracture of membranes.

Vitamin E is also essential for the maintenance of a functional immune system. In vitamin E deficiency there is a decrease in the resistance to infection, in the immune response, in the activation of T lymphocytes, in the production of interleukin 2, and in the phagocytic capacity. Patients receiving lipid emulsion in parenteral nutrition have an increased requirements for vitamin E.

The following examples are to be considered merely as illustrative and non-limiting in nature. It will be apparent to one skilled in the art to which the present invention

pertains that many modifications, permutations, and variations may be made without departing from the scope of the invention.

EXAMPLE 1

This example illustrates the fatty acid composition of structured triglycerides and parenteral nutrition emulsion comprising thereof. As shown in Table 1, medium chain FA, long chain FA, and very long chain FA comprise 45, 50.5, and 4.5% by weight, respectively, of total FA in the structured triglycerides. The ratio of ω-6 to ω-3 fatty acids in the structured triglycerides is 1.75.

Table 1. Fatty acid composition of structured triglycerides

Caproic acid,	**6:0**	**2.5**
Caprilic acid	**8:0**	**30**
Capric acid	**10:0**	**10**
Lauric acid	**12:0**	**2.5**
Palmitic acid	**16:0**	**10**
Stearic acid	**18:0**	**2.5**
Oleic acid	**18:1**	**15**
Linoleic acid	**18:2 ω-6**	**16**
Alpha linolenic acid	**18:3 ω-3**	**7**
Arachidonic acid (AA)	**20:4 ω-6**	**1.5**
Ecosapentaenoic acid (EPA)	**20:5 ω-3**	**1.5**
Docosahexaenoic acid (DHA)	**22:6 ω-3**	**1.5**

Parenteral nutrition emulsion comprising structured triglycerides is then prepared. The composition of the parenteral nutrition is as follows:

Structured triglycerides having a ratio of 1.75 of ω-6 to ω-3 fatty acids - 20% (w/v)

Alpha tocopherol – 1.8 mg/1 gr fatty acids

Phospholipids – 12 gr/liter

Water to complete to 1 liter.

EXAMPLE 2

Synthesis of structured triglycerides

Crude or purified lipase is first coated with lipid surfactant or other enzyme activators, e.g. gum Arabic or polyethylene glycol. A typical enzyme modification and immobilization procedure is as follows: crude enzyme (lipase, phospholipase, protease and glycosidases; protein content approximately 150 mg/L), is dissolved in Tris buffer solution with an appropriate pH, and magnetically stirred at 10° C for 30 min. A lipid surfactant or other enzyme activator (0.5 g) dissolved in ethanol (20 ml) or other solvents is added drop wise into the stirred solution. The resulting enzyme solution is sonicated for 15 min and then vigorously stirred at 10° C for 3 hours. An insoluble organic (20 g such as polypropylene, aluminium stearate or chitin) or inorganic matrix (20 g such as Celite, alumina, silica gel or ceramic support) is added into the stirred enzyme solution. The solution is magnetically stirred for a further 5 hours at 10° C. The precipitate is collected by centrifugation at 12000 rpm or by filtration, and then treated by one of two different methods as follows: (i) the wet precipitate is lyophilized after freezing overnight at -20° C. The formed powder can be directly used for batch enzymatic reactions or granulated for obtaining particulated modified and immobilized enzyme with a particle size of 50-1000 μm. The granulation process is performed using various binding reagents such as starch, methyl or ethyl cellulose, gums, agarose or other binders. For example, the granulation with starch is conducted as follows: Starch solution (4 g starch/20 ml water) is converted to gel at 70° C. The gel is cooled down to 60° C, and then introduced to the modified and immobilized enzyme wet powder. The mixture is homogenized in a high-speed mixer followed by extruding and drying at 40-60° C for 48 hours. The immobilized enzyme is sieved to obtain particles in the range of 50-1000 μm. This particulated enzyme is used mainly in packed columns; (ii) the wet precipitate formed after modification and immobilization is directly granulated with starch or other binding reagents as described above.

The above-described modification, immobilization and granulation procedures are also used in conjunction with ion-exchange resins. The types of resin that may be used include: strong and week basic anion exchange resins, strong and weak acidic cationic exchange resins and weak-polar and apolar ion-exchange resins.

Lipase immobilization through covalent binding is performed as follows: the enzyme is primarily coated with a surfactant and then the lipase-surfactant complex is covalently linked to a Eupergit matrix, which contains active oxirane groups. To this end, crude lipase (1 gram protein) is dissolved in 1 liter Tris or phosphate buffer pH 5.8. The enzyme solution is vigorously stirred with a magnetic stirrer at 10° C for 30 minutes. Sorbitan mono-stearate (0.5 grams) dissolved in 30 ml ethanol are added drop wise to the stirred enzyme solution. The resulting colloidal enzyme solution is sonicated for 10 minutes and then stirred for 3 hours at 10° C. Eupergit C or Eupergit C 250L (125 grams) and 12 ml solution of 5% hydrogen peroxide are added into the enzyme solution and the resulting suspension is gently shaken for 1 minute, and then incubated for 48 hours at 23° C. The precipitate is filtered, washed with Tris or phosphate buffer pH 5.8, and is freeze-dried overnight.

The transesterification reaction is initiated by adding 10 mg immobilized lipase preparation to 10 ml n-hexane that contains 40 mg triglyceride having a fatty acid of 6 to 10 carbon atoms bonded at the position 2 and 35 mg of long or very long fatty acid. The reaction is magnetically stirred at 40° C for 2 to 100 hours. The immobilized enzyme is used repeatedly. Namely, the reaction is continued by leaving the immobilized enzyme in a reaction vessel after reaction, and replacing the reaction mixture with freshly prepared reaction mixture comprising a fatty acid. Next, triglyceride is purified, and transesterification is again performed with another long or very long fatty acid using said purified triglyceride as a starting material.

EXAMPLE 3

Preparation of an emulsion comprising structured triglycerides

800 g of the present triglyceride preparation are prepared in large volume according to the same procedure as in Example 2, 48 g of purified egg yolk lecithin, 100 g of concentrated glycerin, 144 mg of alpha tocopherol, and 40 ml of 0.1 N sodium hydroxide are dispersed with a homogenizer. Distilled water for injection is added to the homogenate to bring to a total liquid volume of 4 liters, which is then emulsified with a high-pressure spraying emulsifier to prepare a lipid emulsion. After filling 200 ml aliquots of said lipid emulsion into plastic bags, the plastic bags are sterilized using high-pressure steam for 20 minutes at 121°C to obtain a nutrition emulsion composition.

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described herein above. Rather the scope of the invention is defined by the claims that follow.

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CLAIMS

1. A structured triglyceride comprising a glycerol backbone having three fatty acid residues esterified thereto, wherein at least one fatty acid residue is selected from the group consisting of C_6-C_{12} fatty acids and active derivatives thereof, and at least one fatty acid residue is selected from the group consisting of C_{14}-C_{18} fatty acids, C_{20}-C_{22} fatty acids, and active derivatives thereof, with the proviso that a C_{18}-C_{22} ω-3 fatty acid residue is not present on the same glycerol backbone together with gamma linolenic acid or dihomogamma linolenic acid.

2. The structured triglyceride according to claim 1, wherein the at least one C_{14}-C_{18} fatty acid is selected from palmitic acid, stearic acid, oleic acid, linoleic acid, and alpha linolenic acid.

3. The structured triglyceride according to claim 1, wherein the at least one C_{20}-C_{22} fatty acid is selected from arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid.

4. The structured triglyceride according to claim 1, wherein the C_{14}-C_{18} fatty acid and the C_{20}-C_{22} fatty acid is selected from ω-3, ω-6, and ω-9 fatty acids.

5. A structured triglyceride comprising a glycerol backbone having three fatty acid residues esterified thereto, wherein at least one fatty acid residue is selected from the group consisting of C_6-C_{12} fatty acids and active derivatives thereof in the internal position of the triglyceride backbone, and at least one fatty acid residue is selected from the group consisting of C_{14}-C_{18} fatty acids, C_{20}-C_{22} fatty acids, and active derivatives thereof in an external position of the triglyceride backbone.

6. The structured triglyceride according to claim 5, wherein the at least one C_{14}-C_{18} fatty acid is selected from palmitic acid, stearic acid, oleic acid, linoleic acid, and alpha linolenic acid.

7. The structured triglyceride according to claim 5, wherein the at least one C_{20}-C_{22} fatty acid is selected from arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid.

8. The structured triglyceride according to claim 5, wherein the C_{14}-C_{18} fatty acid and the C_{20}-C_{22} fatty acid is selected from ω-3, ω-6, and ω-9 fatty acids.

9. A parenteral nutrition emulsion composition comprising a structured triglyceride according to any one of claims 1 to 4.

10. A parenteral nutrition emulsion composition comprising a structured triglyceride according to any one of claims 5 to 8.

11. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein the C_6-C_{12} fatty acids are from about 30 to about 60% by weight of total fatty acids.

12. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein the C_6-C_{12} fatty acids are from about 40 to about 50% by weight of total fatty acids.

13. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein ω-6 fatty acids and ω-3 fatty acids being in a ratio of about 7:1 to 1:1.

14. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein ω-6 fatty acids and ω-3 fatty acids being in a ratio of about 2:1 to 1:1.

15. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein ω-6 fatty acids and ω-3 fatty acids being in a ratio of about 1.75.

16. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein the structured triglyceride is from about 10 to about 40% (w/v) of the composition.

17. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, wherein the structured triglyceride is from about 20 to about 25% (w/v) of the composition.

18. The parenteral nutrition emulsion composition according to any one of claims 9 and 10, further comprising tocopherol.

19. The parenteral nutrition emulsion according to claim 18, wherein the tocopherol is alpha tocopherol.

20. The parenteral nutrition emulsion according to any one of claims 9 and 10, further comprising an emulsifier.

21. The parenteral nutrition emulsion according to any one of claims 9 and 10, further comprising at least one component selected from carbohydrates, vitamins, amino acids, trace minerals, and osmolality modifier.

22. A method of providing nutrition to a subject in need thereof comprising parenterally administering to the subject a parenteral nutrition emulsion composition according to any one of claims 9 to 21.

23. The method according to claim 22, wherein the subject is selected from preterm infants, term infants, critically ill patients, cancer patients, patients suffering from trauma, burns, malnutrition, starvation, aging, and immunosuppression.

24. The method according to claim 23, wherein the subject is selected from preterm infants, term infants, critically ill patients, and AIDS patients.

ABSTRACT

The present invention relates to structured triglycerides, to parenteral nutrition emulsions comprising same, and use thereof. In particular, the invention relates to structured triglycerides comprising at least one medium chain C_6-C_{12} fatty acid and at least one fatty acid selected from long chain C_{14}-C_{18} or very long chain C_{20}-C_{22} fatty acid, preferably each fatty acid being in a predetermined position of the glycerol backbone. The parenteral nutrition emulsions are particularly useful for nourishing preterm and term infants, children, critically ill patients, and cancer patients.